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09/978,191	10/15/2001	Audrey Goddard	GNE.2630P1C4	4728

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EXAMINER

O HARA, EILEEN B

ART UNIT PAPER NUMBER

1646

DATE MAILED: 03/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

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DETAILED ACTION

1. Claims 58-63, 69 and 70 are pending in the instant application. Claims 64-68 have been canceled and claims 58-63 have been amended as requested by Applicant in the Amendment filed October 4, 2004.

Withdrawn Objections and Rejections

2. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Priority Determination

3. Applicant is advised that the instant application can only receive benefit under 35 U.S.C. § 120 or § 119(e) from an earlier application which meets the requirements of 35 U.S.C. § 112, first paragraph, with respect to the now claimed invention.

Applicants' response has clarified that nucleic acid of SEQ ID NO: 505 and encoded protein of SEQ ID NO: 506 (PRO213-3) are the same as the sequences identified as PRO1330 (clone DNA30943) in provisional 60/100,038, which demonstrates a specific and substantial utility for the nucleic acid, as a cancer diagnostic. Pages 61-69 of 60/100,038 demonstrate that this nucleic acid is amplified in a large number of lung tumors, which was corrected for aneuploidy. However, the effective priority date of the instant application is considered to be the filing date of this application, October 15, 2001, because the claimed invention is not supported by either a specific and substantial utility or a well established utility for the claimed polypeptides.

Maintained Rejections

Claim Rejections - 35 USC § 101 and § 112

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims 58-63, 69 and 70 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, for reasons of record in the previous office action, mailed June 2, 2004, at pages 5-9 and below.

Applicants' arguments (pages 18-28, Paper filed Oct. 04, 2004) have been fully considered but are not deemed persuasive.

Applicants traverse the rejection and discuss the legal standard for utility on pages 19-20, and starting on page 21 discuss the proper application of the legal standard. Applicants rely on the gene amplification data for patentable utility for the PRO213-1 protein, and explain the gene amplification assay of Example 114, in which PRO213-1 is amplified more than two fold in three types of human primary lung tumors, which Applicants assert is significant and that the PRO213-1 gene has utility as a diagnostic of lung cancer.

Applicants submit the Declaration by Dr. Audrey Goddard, in which she states that a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer. Applicants assert that as the TaqMan realtime PCR method has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification,

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one of ordinary skill in the art would find it credible that PRO213-1 is a diagnostic marker of human lung cancer.

The Goddard Declaration filed under 37 CFR 1.132, filed Oct. 4, 2004 is insufficient to overcome the rejection of claims 58-63, 69 and 70 as set forth in the last Office action because: while the declaration and supporting references are convincing that the TaqMan realtime PCR method is very sensitive and can identify amplified genes, the claims are drawn to protein encoded by the PRO213-1 gene, and as discussed in the previous office action and below, it is not predictable that gene amplification results in increased mRNA expression, or that increased mRNA expression results in increased protein production.

Applicant argues that the Gygi et al. publication does not support the rejection. Applicant characterizes Gygi et al. as teaching that there is a general trend but no strong correlation between polypeptide expression level and transcript level. Applicant further characterizes Gygi et al.'s conclusions as showing that there is a positive correlation between transcript and polypeptide for most of the 150 yeast polypeptides studied, but the correlation is not linear and thus one cannot accurately predict polypeptide levels from mRNA levels. Applicant concludes that Gygi et al. show that it is more likely than not that a positive correlation exists between mRNA and polypeptide levels. This has been fully considered but is not found to be persuasive. In the instant case, the specification provides data showing a very small increase in **DNA** copy number, approximately **2-fold**, in a few tumor samples for PRO213-1. There is no evidence regarding whether or not the PRO213-1 **mRNA** or **polypeptide** levels are also increased in these tumor samples. Since the instant claims are directed to PRO213-1 **polypeptide**, it was imperative to find evidence in the relevant scientific literature whether or not a small increase in

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DNA copy number would be considered by the skilled artisan to be predictive of increased in mRNA and polypeptide levels. Pennica et al. was cited as evidence showing a lack of correlation between gene (DNA) amplification and elevated mRNA levels. Gygi et al. was cited as providing evidence that polypeptide levels cannot be accurately predicted from mRNA levels, and that variances as much as **40-fold** or even **50-fold** were not uncommon. While Gygi et al. demonstrates that **high levels** of mRNA generally correlate with high levels of protein, it has not been demonstrated that the PRO213-1 mRNA is over-expressed at high levels. The majority of mRNAs at levels of expression other than high levels do not show a correlation with protein levels. Given the small magnitude by which the DNA copy number of PRO213-1 is increased, and the evidence provided by Gygi et al. and Pennica et al., it is clear that one skilled in the art would not assume that a small increase in gene copy number would correlate with significantly increased mRNA or polypeptide levels, and that it is not more likely than not that a higher level of mRNA correlates with a higher level of protein. One skilled in the art would do further research to determine whether or not the PRO213-1 polypeptide levels increased significantly in the tumor samples. The requirement for such further research requirements makes it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which the court held that:

“The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility”, “[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to

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be a broad field”, and “a patent is not a hunting license”, “[i]t is not a reward for the search, but compensation for its successful conclusion.”

Applicant refers to three additional articles (Orntoft et al., Hyman et al. and Pollack et al.) as providing evidence that gene amplification generally results in elevated levels of the encoded polypeptide. Applicant characterizes Orntoft et al. as teaching in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Applicant characterizes Hyman et al. as providing evidence of a prominent global influence of copy number changes on gene expression levels. Applicant characterizes Pollack et al. as teaching that 62% of highly amplified genes show moderately or highly elevated expression and that, on average, a 2-fold change in DNA copy number is associated with a 1.5-fold change in mRNA levels. This has been fully considered but is not found to be persuasive. Orntoft et al. appear to have looked at increased DNA content over large regions of chromosomes and comparing that to mRNA and polypeptide levels from the chromosomal region. Their approach to investigating gene copy number was termed CGH. Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The instant specification reports data regarding amplification of individual genes, which are not likely to be in a chromosomal region which is highly amplified, given the low Δ CT values. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p. 40). This analysis was not done for PRO213-1 in the instant specification. That is, it is not clear whether or not PRO213-1 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance of Orntoft et al. is not clear. Hyman et al. used the same CGH approach in their research. Less

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than half (44%) of highly amplified genes showed mRNA over-expression (abstract).

Polypeptide levels were not investigated. Therefore, Hyman et al. also do not support utility of the claimed polypeptides. Pollack et al. also used CGH technology, concentrating on large chromosome regions showing high amplification (p. 12965). Pollack et al. did not investigate polypeptide levels. Therefore, Pollack et al. also do not support the asserted utility of the claimed invention. Importantly, none of the three papers reported that the research was relevant to identifying probes that can be used as cancer diagnostics. The three papers state that the research was relevant to the development of **potential** cancer therapeutics, but also clearly imply that much further research was needed before such therapeutics were in readily available form. Accordingly, the specification's assertions that the claimed PRO213-1 proteins have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

The Polakis declaration under 37 CFR 1.132 filed Oct. 4, 2004 is insufficient to overcome the rejection of claims 58-63, 69 and 70 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action for the following reasons: In the declaration, Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor cell markers useful as targets for cancer diagnostics and therapeutics, and that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to approximately 30 of the tumor antigen polypeptides have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in polypeptide levels. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the

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encoded polypeptide. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule. This has been fully considered but is not found to be persuasive. First, it is important to note that the instant specification provides no information regarding increased mRNA levels of PRO213-1 in tumor samples relevant to normal samples. Only gene amplification data was presented. Therefore, the declaration is insufficient to overcome the rejection of claims 58-63, 69 and 70 based upon 35 U.S.C. §§ 101 and 112, first paragraph, since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels, and not gene amplification levels and polypeptide levels. Furthermore, the declaration does not provide data such that the examiner can independently draw conclusions. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (2003, *Journal of Proteome Research* 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published

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role in the disease (see discussion section). PRO213-1 does not display a 10-fold or greater amplification, according to the specification.

Applicants further assert that even if one assumes that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, a polypeptide encoded by a gene that is amplified in cancer would still have a specific and substantially utility, and provides the declaration by Dr. Avi Ashkenazi. Dr. Ashkenazi explains that even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment, in that if the gene product is over-expressed in some tumor types but not others, this would enable more accurate tumor classification and hence better determination of suitable therapy, and additionally, if a gene is amplified by the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

The Ashkenazi declaration filed under 37 CFR 1.132 filed Oct. 4, 2004 is insufficient to overcome the rejection of claims 58-63, 69 and 70 based upon lack of utility as set forth in the last Office action because: it has not been demonstrated that the protein of the instant invention is differentially expressed in different tumors. If it was, the protein would have a specific and substantial utility for tumor classification, but the mere assertion that it may be differentially expressed does not provide a specific and substantial utility, and is an invitation to experiment. The argument that if a gene is amplified but the gene product is not over-expressed, the clinician would accordingly decide not to treat a patient with agents that target the gene product is also insufficient to overcome the rejection of the claims. If a specific gene product was known to be

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involved in cancer and if there were known compounds that could be used to target the gene product, this would be an acceptable utility. However, the gene product of the instant invention has not been demonstrated to be involved in cancer. Over-expression of a gene product in a cancer cell does not necessarily mean that the gene product is involved in the cancer and that targeting the gene product would be therapeutic. Additionally, there are no known compounds that would target the gene product.

Applicants provide the Hanna et al. reference to support the Declaration of Dr. Ashkenazi. The Hanna reference is not applicable to the instant fact situation, as it deals with a known tumor associated gene, and not with a prospective analysis of the type found in this specification.

The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed polypeptides. For all of these reasons, the rejections are maintained.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5.1 Claims 58-63, 69 and 70 also remain rejected under 35 U.S.C. 112, first paragraph.

Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

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5.2 Claims 58-62, 69 and 70 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants traverse the rejection and assert that the specification discloses a substantial, specific and credible utility for the PRO213-1 polypeptide, and have additionally amended claims 58-62 to “wherein the nucleic acid encoding the polypeptide is amplified in lung tumors”. Applicants submit that since the claimed genus is now characterized by a combination of structural and functional features, any person of skill would know how to make and use the invention without undue experimentation.

Applicants’ arguments have been fully considered but are not deemed persuasive. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factors present in the claim are functional, in that the protein of SEQ ID NO: 506 is encoded by a nucleic acid that is amplified in lung cancer. The specification discloses only a single sequence, SEQ ID NO: 506, that meets the limitations of the claims. It is clear that while there *could* be additional polypeptides that meet the limitations of the claims, that conception of such polypeptides has not occurred, and cannot occur until their actual isolation, as it is not predictable what additional mutations in SEQ ID NO: 506 would occur in nature and further be associated with lung cancer. As previously stated,

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one cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483.

In *Fiddes*, claims directed to mammalian FGF'S were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. In this case, applicants have described a single sequence asserted to be associated with lung cancer, and propose to obtain coverage for all related sequences that have a similar association. There is no description of that class of compounds. This case is also analogous to that in *Amgen v. Chugai*, 18 USPQ 2d 1017 (1991), in which it was found that conception may not be achieved until reduction to practice in cases involving cloning genes. In this case, applicants have no conception of which of the thousands of possible polypeptides and nucleic acids that could encode the protein of SEQ ID NO: 506 would meet the limitation of being amplified in lung cancer.

Vas-cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. Chugai*

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Pharmaceutical Co. L td., 18 USPQ2d 1016.

Therefore, polypeptides comprising the sequence set forth in SEQ ID NO: 506, but not the full breadth of the claims meet the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

Rejections over Prior Art
Claim Rejections - 35 USC § 102 and § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6.1 Claims 58-63 and 69 remain rejected under 35 U.S.C. 102(e) as being anticipated by Holtzman et al., U.S. Published Patent Application 20020028508, effective priority date April 23, 1998 (09/065,363), for reasons of record in the previous office action, mailed June 2, 2004, at pages 13 and 14.

6.2 Claims 58-62, 69 and 70 remain rejected under 35 U.S.C. 102(e) as being anticipated by Sheppard et al., U.S. Published Patent Application 20030166907, effective priority date June 18, 1997 (09/050,143), for reasons of record in the previous office action, mailed June 2, 2004, at pages 14-15.

6.3 Claim 70 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Holtzman et al., U.S. Published Patent Application 20020028508, effective priority date April 23, 1998

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(09/065,363), in view of Hopp et al., U.S. Patent Number 5,011,912, April 1991, for reasons of record in the previous office action, mailed June 2, 2004, at pages 16-17.

Applicants traverse the rejections and submit that in order to overcome the 35 U.S.C. 102(e) rejections and support the priority claim, the Declaration by Goddard, Godowski, Gurney and Wood simply need to provide a disclosure commensurate in scope with the disclosure in both Holtzman et al. and Sheppard et al.

The declaration of Goddard, Godowski, Gurney and Wood filed on October 4, 2004 under 37 CFR 1.131 has been considered but is ineffective to overcome the Holtzman et al. or Sheppard et al. references. The Holtzman et al. reference is a U.S. patent application publication of an abandoned application, which has a continuation (20050019810) that claims the rejected invention. The Sheppard et al. reference is a U.S. patent application publication currently pending and claiming the polypeptide of SEQ ID NO: 2. An affidavit or declaration is inappropriate under 37 CFR 1.131(a) when the reference is claiming the same patentable invention, see MPEP § 2306. If the references and this application are not commonly owned, the references can only be overcome by establishing priority of invention through interference proceedings. See MPEP Chapter 2300 for information on initiating interference proceedings. If the references and this application are commonly owned, the reference may be disqualified as prior art by an affidavit or declaration under 37 CFR 1.130. See MPEP § 718. Additionally, the declaration of Goddard, Godowski, Gurney and Wood declaration filed on October 4, 2004 is unsigned.

It is believed that all pertinent arguments have been answered.

Conclusion

7. No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (571) 272-0829.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

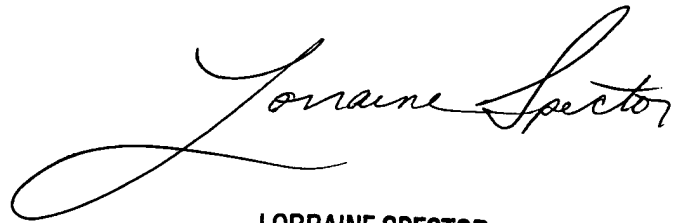
Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

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Eileen B. O'Hara, Ph.D.

Patent Examiner

A handwritten signature in black ink that reads "Lorraine Spector". The signature is written in a cursive style with a large, looping initial "L".

**LORRAINE SPECTOR
PRIMARY EXAMINER**